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EXAMINER	
MARSCHEL, A	

ART UNIT	PAPER NUMBER
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DATE MAILED: 12/28/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

2-3-95
6-7-95
9-28-95

☒ This application has been examined ☒ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. (18 sheets)
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 283-328 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-282 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 283-328 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

AM
PTOL-326 (Rev. 2/93)
08/486,069

It is noted that a Petition to revive the parent application to the instant application has been granted including the mailing of that decision on 3/20/95.

Applicants' amendments, filed 2/3/95, 6/7/95, and 9/28/95, has been entered.

Enclosed is two IDSs, filed 6/28/93 and 9/28/95, which have been executed. Several citations on the 6/28/93 IDS have been lined through as no copies were therewith submitted. On the 9/28/95 IDS the application serial number 255,223 is lined through since this is unpublished. Such unpublished disclosures cannot be cited as prior art on a PTO Form 1449. On said 9/28/95 IDS several other citations are lined through because either they are duplicates from the 6/28/93 IDS or that no copy of the reference was submitted for consideration.

Applicants' arguments and amendments; filed 2/3/95, 6/7/95, and 9/28/95; have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. They constitute the complete set presently being applied to the instant application.

If applicant desires priority under 35 U.S.C. § 120 based upon a parent application, specific reference to the parent application must be made in the instant application. It is noted that this appears as the first sentence of the specification following the title. Status of the parent application (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "Patent No." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "abandoned" should follow the filing date of the parent application. It is noted that citation of serial number

06/674,352 and its status has not been included in this first paragraph even though it is in the parentage line.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

The limitations directed to the covalent attachment of a Sig moiety to a nucleotide base limited to positions other than C^5 of pyrimidines, C^8 of purines, or C^7 of deazapurines as presently given in claim 284 is NEW MATTER. No such negative limitations which are inclusive of numerous other base modification locations are cited in the specification. The presently pending claims dependent from claim 284 also contain this NEW MATTER due to their direct or indirect dependence from claim 284. It is noted that none of these dependent claims are limited so as to not contain said NEW MATTER limitation. Even claims such as 310 contain this limitation in that its Sig attachment limitation only limits the nucleotide (iii) selection but that the claim lacks wording such that this (iii) selection is the only labeled nucleotide type.

Claims 284-328 are rejected, as discussed above, under 35

U.S.C. § 112, first paragraph, for the reasons set forth in the above objection to the specification.

Claims 284-328 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a scope of covalent attachment sites of the cited "Sig" moiety to bases of nucleic acids wherein said sites are either the N^2 of guanine, the N^6 of adenine, the N^4 of cytosine, or the C^6 of uracil. A thorough review of the disclosure as filed has revealed that the chemistry by which nucleic acid bases may be modified so as to attach a "Sig" moiety only is disclosed for the above four attachment sites within the scope of claims 284 etc. For example, the instant disclosure does not discuss in any way the preparation of N-1 or N-3 modified purines or N-3 or C-2 modified pyrimidines. It is noted that claims 284 etc. are already limited in that certain other, non-base, attachment sites on purines, pyrimidines, and deazapurines are not within the scope of the claims for the at least one modified base in probes used in the claimed methods. It is also noted that certain generalized labeling methods are instantly disclosed such as the formaldehyde coupling of cytochrome C as a bridge between biotin and a nucleic acid molecule on page 58 but that such generalized labeling of a nucleic acid probe lacks both instant disclosure as well as predictability as to where the attachment site is on the probe and therefore fails to predictably form attachments as instantly claimed and thus is deemed to fail to enable the broad scope of specific base modifications of the instant claims. Ruth

is herein cited as summarizing the lack of knowledge at the time of the instant filing regarding the preparation of nucleic acid hybridization probes which contain a signalling moiety. The earliest disclosure of said summary of Ruth is 2/22/83 which is the filing date of the earliest parent thereof and which is also less than a year after the filing date of the instant application. This therefore summarizes the lack of broad hybridization probe preparatory knowledge even after the instant filing date. Ruth summarizes the preparatory knowledge for signal moiety containing labeled probes in column 1, line 43, through column 3, line 45. As cited therein nucleic acid hybridization probes may be prepared either chemically or enzymatically. Enzymatic synthesis using nick translation is discussed wherein certain base modifications have been incorporated into probes but limited in use due to several factors. One of these factors is that only certain modifications may be incorporated by enzymes. Ward et al.(P/N 4,711,955) summarize the factors that were viewed as limitations on modified nucleotides in column 6, line 36, through column 7, line 17, and thereinafter discuss specific base modifications with detailed and lengthy chemical steps. Ruth at column 3, lines 26-45, also summarizes that chemical synthesis has not been disclosed in the prior art as incorporating modified or reporter group containing nucleotides. Further consideration of Ruth reveals that specific base modifications are therein disclosed such as at column 10, line 57, through column 20 which are accomplished via a lengthy

series of detailed reactions including the masking and unmasking of reactive side groups to prevent unwanted modifications. Ruth and Ward et al. are deemed representative of those skilled in the art at about the time of the instant filing date of the instant disclosure. In summary, those skilled in the art at the time of filing of the instant invention viewed the preparation of signal moiety containing nucleic acid probes as lengthy and detailed procedures that were discussed as being accomplished only for certain specific base modifications. It is noted that Ruth or Ward et al. only disclose base modifications at the following sites: C-8 of purines and the C-5 of pyrimidines, N^6 of adenosine, and N^2 of guanosine, and N^4 of cytosine, and C-7 of 7-deazapurines. This documents the lack of enablement of most specific base modifications without detailing lengthy preparatory procedures for those skilled in the art at the time of the instant filing date. Therefore it is deemed undue experimentation to prepare base modified nucleic acid hybridization probes wherein the site of base modifications is other than the N^2 of guanine, the N^6 of adenine, the N^4 of cytosine, or the C-6 of uracil within the scope of instant claims 240 etc. It is again noted that the instant claims are limited so that base modifications at the C-8 of purines, the C-5 of pyrimidines, and the C-7 of 7-deazapurines are not within their scope. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claims 284-328 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited

to "SM" moieties which are either ribose or deoxyribose. It is noted that claim 284, lines 13-15, cite "PM" attachment points when the nucleotide compound is either a deoxyribonucleotide or ribonucleotide but does not therein limit the "SM" moiety to a sugar moiety that is present in either of these nucleotide types. Thus, the scope of "SM" is only presently limited in claims 284 etc. to being a "sugar moiety" which is much broader in scope than that of ribose or deoxyribose. It is noted that there is no instant discussion as to how to practice the synthesis of nucleotides with "SM" moieties other than that of ribose or deoxyribose. For example, how does someone wishing to utilize glucose as "SM" practice the instant claims? It is noted that in order to broadly practice sugar moieties usage both the synthesis of "PM" attachment is required as well as the "Sig" attachment. Additionally hybridization between the nucleic acid of interest and the oligo- or polynucleotide must still be permitted. No guidance whatsoever has been instantly set forth directed to accomplishing this broad sugar moiety practice other than that directed to ribose or deoxyribose sugars. It is noted additionally that the numerous examples given in the specification do not include any sugar practice other than ribose or deoxyribose. In the above scope rejection directed to base labeling practice the need for detailed and lengthy procedures to enable the person skilled in the art to prepare nucleotide analogs as well as their incorporation into polymers is summarized. These disclosures include complex chemical

protection requirements including those directed to sugar side group protection as well as considerations such as whether enzymes would recognize and incorporate nucleotides into polymers or not as well as other considerations as discussed above. Thus, it is deemed undue experimentation to practice nucleotide compound and polymers containing these compounds without such detailed and lengthy procedural guidance. In summary, such detailed and lengthy guidance is instantly set forth only for "SM" practice directed to ribose or deoxyribose and it is deemed undue experimentation to practice "SM" moieties other than ribose and deoxyribose given the limited instant disclosure. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claims 283-328 are rejected, as discussed below, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is noted that applicants state in their REMARKS on page 13, filed 9/28/95 that claim 283 has been canceled. Consideration of the various amendments of record has revealed no such cancellation. Claim 283 still therefore remains pending and is vague and indefinite in that it depends from a cancelled claim.

Claim 284, part (b), cites the detection of the presence of "oligo- or polynucleotides which have hybridized to said nucleic acid of interest" but is vague and indefinite when considered in view of part (a) of the claim. Said part (a) cites the practice

of "permitting hybridization..." without any selectivity or specificity directed to preventing hybridization to nucleic acids that are not the "nucleic acid of interest". Thus, such "permitting" practice is reasonably interpreted as inclusive of all levels of stringency including conditions where hybridization is permitted to not only "nucleic acid of interest" but also to other nucleic acids that may be only 90% complementary, 70% complementary, or even only 20% complementary, etc. to the "oligo- or polynucleotide" cited in part (a). With this broad complementarity practice possible within the scope of part (a), what is meant by applicants' citation of the detecting practice of part (b)? Do applicants mean that selectivity or specificity is to be practiced at the detection step and not at the hybridization step? This suggests that the detecting step is not just a detecting step but is also inclusive of some selection practice. Such a selection practice is not given in step (b) as presently worded. It is noted that the commonly performed practice of a hybridization assay is to control the hybridization step, herein step (a) rather than step (b), so as to be selective as desired. Then the detection step is only directed to the detection of a signal which is then indicative of the presence of the "nucleic acid of interest" in the sample. This, however, is not how claim 284 is presently worded. This unclarity causes even more concern regarding claims such as 324 or 325 which are directed to genetic disorder detection. Additionally there is no mention of the "Sig" moiety in the detection practice of step (b)

whereas it is the only "detectable" moiety that is cited in part (a). Do applicants intend that the detection practice of part (b) is inclusive of detection without use of the "Sig" moiety from part (a)? Alternatively, if detection of the "Sig" moiety of part (a) is intended to be the manner of detection of hybridization in part (b), why is part (b) silent regarding said "Sig" moiety? Clarification is requested as to what applicants mean for the metes and bounds of parts (a) and (b) regarding how the presence of the "nucleic acid of interest" is indicated in the sample versus nucleic acids that are not of interest and what signal is determinative of said presence. Do applicants mean to include some selectivity in either of parts (a) or (b) and, if so, which part or parts? This unclarity is present in all of the instantly depending claims due to their direct or indirect dependence from claim 284.

Claims 284 and those dependent therefrom directly or indirectly all are vague and indefinite because the metes and bounds of the positions on the base at which the Sig moiety is covalently attached is not commensurate with the various disclosures in the specification. See, for example, the directive on page 53, lines 1-4, which limits the modifications as to not interfering with the formation of a double-helix which is not recited in the claims.

In claim 293, lines 2-3, the phrase "complexed with or attached to a sugar or polysaccharide binding protein" is cited which makes the claim vague and indefinite because it is unclear

whether the phrase "to a sugar" within the longer cited phrase is meant to modify the "binding protein" characteristic or whether it is meant to indicate the the first cited sugar residue in the claim may be complexed with or attached to another sugar independent of the presence of a binding protein. Clarification of what is meant regarding the metes and bounds of claim practice by the phrase "to a sugar" is requested. This rejection also applies to claims 294-296 which are rejected due to their dependence from claim 293.

Claim 327 at its last line is vague and indefinite regarding what is meant regarding the practice of the phrase "5' addition of Sig". Does this mean that the uracil moiety cited in line 5 is modified at its 5' moiety or does it mean that the "Sig" cited in said last line is limited to moieties that contain a "5'" attachment point which is the point of attachment to anywhere on the cited uracil? Clarification as to what "5' position" is meant on what moiety is requested.

The disclosure is objected to because of the following informalities:

On page 56, line 14, the concentration of tris base appears to be miscapitalized.

On page 56, line 18, and elsewhere, a temperature is cited without a type of scale designation.

The use of the trademark SEPHADEX (page 56, line 22, and elsewhere) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic

terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

On page 57, line 10, the chemical moiety "diisopropylaminocarboimide" appears to be misspelled. A similar misspelling is present on page 81, line 20.

On page 59, line 15, a double dash is present in a chemical formula that is confusing as to what is meant thereby.

On page 69, lines 4 and 23, a space is present before "DNA" that probably should be amended to contain the word "lambda".

On page 79, line 2, an enzyme is named "Calf intestine alkaline phosphate" which is confusing in that "phosphate" appears to be incorrect in context.

Numerous other incorrect spellings etc. are present in the instant specification. Applicants are requested to review the entirety of the disclosure and correct these numerous errors by amendment.

Appropriate correction is required.

Two Engelhardt et al. patents have been cited on the enclosed PTO Form 892 as having been considered in that they are related to the instant application as being derived from the same earliest filed parent application as the instant application.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in

the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 305-3014 or (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

December 22, 1995

Ardin H. Marschel

ARDIN H. MARSCHEL
PATENT EXAMINER
GROUP 1800